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(54) Intermediates and process for the preparation of an antiviral agent

(57) (1R,trans) Diprotected 3-methylene-1,2-cyclopropanedimethanol is oxidized to an optically active diol intermediate which is then cyclized to an orthoester intermediate, and then converted to the (2S-trans)diprotected 2,3-bis(hydroxymethyl)cyclobutanone. This cyclobutanone is useful as an intermediate in the preparation of the antiviral agent [1R-(1α,2β,3α)]-2-amino-9-[2,3-bis(hydroxymethyl)cyclobutyl]-1,9-dihydro-6H-purin-6-one.

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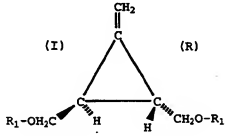
Description

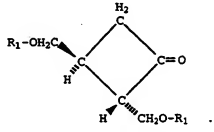
This invention is directed to an improved process for converting the optically active compound of the formula

(I) (R)



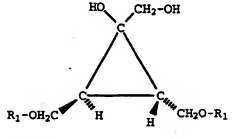
to the optically active cyclobutanone of the formula

(IV)



In the first step of the process of this invention, the 3-methylene starting material of formula I is oxidized to the diol of the formula

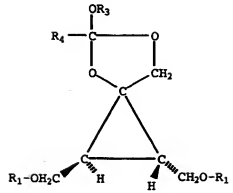
(II)



A suitable oxidizing reagent for this reaction is osmium tetroxide.

In the next step of the process of this invention, the diol of formula II is converted to the cyclic orthoester of the formula

(III)



This conversion is performed by treating the diol of formula II with a trimethyl or triethyl orthoester in the presence of a weak acid catalyst.

The cyclic orthoester of formula III is then converted to the optically active cyclobutanone of formula IV by treating with a Lewis acid catalyst.

R_1 in the above formulas is a hydroxy protecting group. Suitable hydroxy protecting groups include silyl groups such as t-butyldimethylsilyl, t-butyldiphenylsilyl, (triphenylmethyl)dimethylsilyl, methyldiisopropylsilyl, and triisopropylsilyl, benzyl and substituted benzyl grous such as p-methoxybenzyl, triphenylmethyl and substituted triphenylmethyl groups such as 4-methoxy substituted triphenylmethyl and 4,4-dimethylsubstituted triphenylmethyl, and acyl groups of the formula

wherein R_2 is straight or branched chain alkyl of 1 to 6 carbons or phenyl.

R_3 is methyl or ethyl.

R_4 is straight or branched chain alkyl of 1 to 6 carbons or phenyl.

This invention is also directed to the novel intermediates of formulas II and III shown above.

According to the process of this invention a solution of the diprotected resolved compound of formula I in an organic solvent is treated with a oxidizing agent to give the diol of formula II. The preferred oxidizing agent is osmium tetroxide employed in an aqueous solution. Suitable organic solvents for the diprotected resolved compound of formula I include acetone, which is preferred, ethyl acetate, dichloromethane, etc.

Preferred features of the process will now be described. The osmium tetroxide may be employed in catalytic amounts by including a cooxidant in the reaction mixture to regenerate the spent osmium tetroxide. 4-Methylmorpholine N-oxide is the preferred cooxidant. When the cooxidant is employed, the osmium tetroxide is utilized in an aqueous solution containing from about 0.2 mole percent to about 0.8 mole percent, preferably about 0.5 mole percent.

The reaction of diprotected resolved compound of formula I to the diol of formula II may be performed at room temperature.

In the next step of the process of this invention, the diol of formula II is converted to the spiro compound of formula III. A solution of the diol of formula II in an organic solvent such toluene, which is preferred, benzene, etc., may be treated with a trimethyl or triethyl orthoester of the formula

$$R_4\text{-}C\text{-}(OR_3)_3$$

such as trimethyl orthoacetate, which is preferred, trimethyl orthobenzoate, trimethyl orthobutyrate, triethyl orthoacetate, triethyl orthopropionate, trimethyl orthovalerate, etc. Preferably, the reaction is performed in the presence of a weak acid catalyst such as pyridium p-toluenesulfonate.

The reaction of the diol of formula II to the spiro compound of formula III may be performed at room temperature

preferably under an inert atmosphere.

In the next step of the process of this invention, the spiro compound of formula III is converted to the optically active diprotected cyclobutanone of formula IV. A solution of the spiro compound of formula III in an organic solvent such as toluene, ethylacetate, or dichloromethane, which is preferred, may be treated with a Lewis acid catalyst.

Suitable Lewis acid catalysts for this reaction include boron trifluoride etherate, which is preferred, trimethylsilyl trifluoromethanesulfonate, boron trichloride, boron tribromide, diethylaluminum chloride, ethylaluminum dichloride, aluminum trichloride, titanium tetrachoride, tin tetrachloride, tin trichloride, etc.

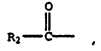
The reaction of the spiro compound of formula III and the Lewis acid catalyst may be performed at low temperatures, preferably at about 0°C. The spiro compound of formula III can be utilized in crude form. The resulting diprotected optically active cyclobutanone product of formula IV may be purified by conventional techniques following completion of the reaction.

The diprotected dimethanol compound of formula I may be prepared by treating (1R-trans)-3-methylene-1,2-cyclopropanedimethanol with a protecting agent such as a chloride of the formula

(V) R_1-Cl

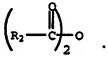
when R_1 is benzyl, substituted benzyl, triphenylmethyl, substituted triphenylmethyl, a hindered silyl, or an acyl group of the formula

(VI)



or by treating with an anhydride of the formula

(VII)

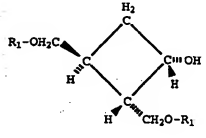


The preferred R_1 protecting group in the compound of formula I is benzoyl which may be prepared by reacting (1R-trans)-3-methylene-1,2-cyclopropane-dimethanol with benzoic anhydride as described in Example 1(c) of U.S. Patent 5,185,463.

The optically active cyclobutanone of formula IV can be converted to the antiviral agent [1R-(1α,2β,3α)]-2-amino-9-[2,3-bis(hydroxymethyl)-cyclobutyl]-1,9-dihydro-6H-purin-6-one by known methods.

As taught by Bisacchi et al. in U.S. Patent 5,064,961 and Singh et al. in European Patent Application 572,209, the optically active cyclobutanone of formula IV can be treated with a reducing agent to give the optically active cyclobutanol of the formula

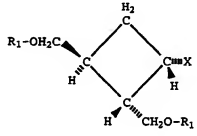
(VIII)



Suitable reducing reagents include hydride reagents such as lithium tri-sec-butylborohydride, lithium trisiamylborohydride, diisobutylaluminum hydride and the like, hindered borane reducing agents such as dicyclohexylborane, disiamylborane, and the like, dialkylaluminum chlorides such as diisobutylaluminum chloride, alkylaluminum dichlorides such as isobutylaluminum dichloride, trialkylaluminum compounds such as triisobutylaluminum and iridium tetrachloride in the presence of phosphorous acid.

The optically active cyclobutanol of formula VIII may then be converted to the optically active compound of the formula

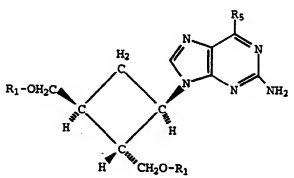
(IX)



wherein X is a leaving group such as chloro, bromo, iodo, an aryl sulfonyloxy group such as p-toluenesulfonyloxy, an alkyl sulfonyloxy group such as methanesulfonyloxy, a substituted alkyl sulfonyloxy group, preferably a perfluoroalkanesulfonyloxy group such as trifluoromethanesulfonyloxy, a nitro substituted aryl sulfonyloxy group such as p-nitrobenzenesulfonyloxy, or fluorosulfonyloxy as taught by Bisacchi et al. in U.S. Patent 5,064,961 and European Patent Application 579,421. For example, when X is a perfluoroalkane sulfonyloxy group, the cyclobutanol of formula VIII is treated with the perfluoroalkanesulfonic anhydride such as trifluoromethanesulfonic anhydride in an inert solvent such as dichloromethane in the presence of a base such as pyridine. When X is a nitro-substituted aryl sulfonyloxy group as p-nitrobenzenesulfonyloxy, the cyclobutanol of formula VIII is reacted with a nitro-substituted aryl sulfonating reagent such as p-nitrobenzenesulfonyl chloride in pyridine or in an inert solvent such as dichloromethane or chloroform containing a base such as pyridine or triethylamine. When X is fluorosulfonyloxy, the cyclobutanol of formula VIII is reacted with fluorosulfonic anhydride in pyridine or in an inert solvent such as dichloromethane or chloroform containing a base such as pyridine or triethylamine.

The optically active compound of formula IX can then be treated with a protected guanine such as 2-amino-6-benzyloxypurine, 2-amino-6-methoxyethoxypurine, 2-amino-6-chloropurine as taught by Bisacchi et al. in U.S. Patent 5,064,961 to give the optically active compound of the formula

(X)

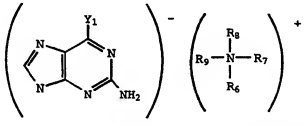


wherein R_5 is a group which can be converted into a 6-oxo-substituent such as a protected hydroxy or a chloro. Removal of the R_1 protecting groups and conversion of R_5 to a 6-oxo gives the desired antiviral agent [1R-(1α,2β,3α)]-2-amino-9-[2,3-bis(hydroxymethyl)cyclobutyl]-1,9-dihydro-6H-purin-6-one. In the preferred embodiment of U.S. Patent 5,064,961, Example 1, the R_1 groups are benzoyl and R_3 is benzyloxy and the intermediate of formula X is treated with a solution of sodium methoxide in methanol to remove the R_1 benzoyl groups and then treated with hydrochloric

acid in aqueous methanol to remove the 6-benzyl protecting group and give the desired product.

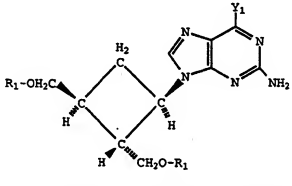
An alternate procedure for converting the optically active intermediate of formula IX to the desired antiviral agent is taught by Bisacchi et al. in European Patent Application 579,421. In this procedure, the intermediate of formula IX is treated with a purine salt of the formula

(XI)



wherein Y_1 is iodo, bromo or chloro and R_6, R_7, R_8 and R_9 are independently straight or branched chain alkyl of 1 to 10 carbons or substituted alkyl of 1 to 10 carbons wherein said substituent is selected from alkoxy of 1 to 6 carbons and aryl, to give the optically active compound of the formula

(XII)



Removal of the R_1 protecting groups and conversion of Y_1 to a 6-oxo yields the desired antiviral agent [1R-(1α,2β, 3α)]-2-amino-9-[2,3-bis(hydroxymethyl)-cyclobutyl] -1,9-dihydro-6H-purin-6-one. In the preferred embodiment of European Patent Application 579,421, the purine salt of formula XI is 6-iodo-9H-purin-2-amine, ion (1-), triethyl(phenylmethyl)ammonium (1:1) salt or 6-iodo-9H-purin-2-amine, ion (1-), tetrabutylammonium (1:1) salt, R_1 is benzoyl, and the intermediate of formula XII is treated with a solution of sodium methoxide in methanol to remove the R_1 protecting groups and convert the 6-iodo to a 6-methoxy followed by treatment with hydrochloric acid to convert the 6-methoxy to a 6-oxo.

The following example is illustative of the invention.

Example 1

(2S-trans)-2,3-Bis[(benzoyloxy)methyl]cyclobutanone

a) (1S-trans)-3-Hydroxy-1,2,3-cyclopropanetrimethanol, α^1, α^2-dibenzoate

Water (9.6 ml) was added to a solution of (1R-trans)-3-methylene-1,2-cyclopropanedimethanol, dibenzoate in acetone (80 ml) at room temperature under an argon atmosphere. To the resulting solution was added a 60 weight percent aqueous solution of 4-methylmorpholine N-oxide (8.1 ml, about 9.15 g. of solution containing about 5.49 g of 4-meth-

ylmorpholine N-oxide, 46.87 mmole) followed by a 4% aqueous solution osmium tetroxide (0.98 ml, about 0.154 mmole, 0.005 eq., 0.5 mole%). The resulting mixture was stirred at room temperature under argon in the dark. The reaction was monitored by TLC analysis. After stirring at room temperature for 22 hours, water (15 ml) was added, followed by sodium metabisulfite (8.0 g, 42.08 mmole). After stirring for about 10 minutes, magnesium silicate (6 g) was added. After stirring for about 15 minutes, the resulting mixture was filtered through a bed of magnesium silicate (18 g) and the filter bed was thoroughly washed with acetone and ethyl acetate. The filtrate was partially concentrated and additional ethyl acetate was added (final volume about 400 ml). The resulting solution was washed with water: 1N hydrochloric acid (5:2, 70 ml), 1N hydrochloric acid (3 x 50 ml), 1N sodium bicarbonate (50 ml) and brine. After drying over magnesium sulfate, the solvent was removed at reduced pressure to give the desired product as a pale yellow solid which was dried under vacuum (11.05 g).

b) (1S,2S)-5-Methoxy-5-methyl-4,6-dioxaspiro-[2.4]heptane-1,2-dimethanol, dibenzoate

To a suspension of the product from part (a) (1.07 g, 3.0 mmole) in anhydrous toluene (10 ml) at room temperature under argon was added trimethyl orthoacetate (0.57 ml, 4.5 mmole, 1.5 eq.) and pyridinium p-toluenesulfonate (11.5 mg, 0.046 mmole, 1.52 mole %). The resulting suspension was stirred at room temperature for 70 minutes, a clear solution was obtained after about 30 minutes. The resulting mixture was concentrated at reduced pressure to give crude (1S,2S)-5-methoxy-5-methyl-4,6-dioxaspiro-[2.4]heptane-1,2-dimethanol, dibenzoate as a nearly colorless oil.

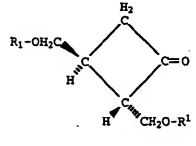
c) (2S-trans)-2,3-Bis[(benzoyloxy)methyl]-cyclobutanone

The crude product from part (b) was dissolved in anhydrous dichloromethane (10 ml). After cooling to about 0°C (ice bath), boron trifluoride etherate (40 µl, 0.325 mmol, 0.108 eq.) was added. After stirring at about 0°C for one hour, the reaction mixture was diluted with ethyl acetate. The resulting solution was washed with 1N hydrochloric acid, 1N sodium bicarbonate, and brine. After drying over magnesium sulfate, the solvent was removed at reduced pressure to give 960 mg of crude product as a colorless solid.

This crude product was dissolved with heating in 2-propanol (5 ml). After cooling to room temperature, the mixture was placed in a refrigerator (about 4°C). After standing in the cold for 4 hours, ice cold 2-propanol (5 ml) was added so as to obtain a pourable mixture. The product was collected by filtration, washed with ice cold 2-propanol, and dried under vacuum to give 890 mg of pure (2S-trans)-2,3-bis[(benzoyloxy)methyl]cyclobutanone as a colorless, fluffy solid. TLC (silica gel, ethyl ether: hexane (6:4) R_f = 0.32; (silica gel, toluene: ethyl ether, 84:16) R_f = 0.41.

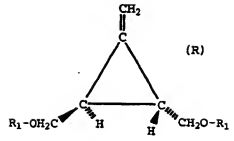
Claims

1. A process for preparing the optically active cyclobutanone of the formula

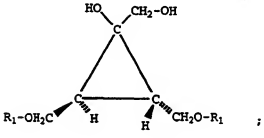


wherein R_1 is a hydroxy protecting group which comprises:

a) oxidizing the optically active 3-methylene compound of the formula

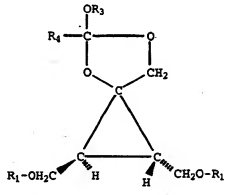


with osmium tetroxide to give the optically active diol of the formula

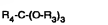


;

b) converting the diol product from step (a) to the cyclic orthoester of the formula



by treating the product from step (a) with a trimethyl or triethyl orthoester of the formula



in the presence of a weak acid catalyst wherein R_3 is methyl or ethyl and R_4 is straight or branched chain alkyl of 1 to 6 carbons or phenyl; and

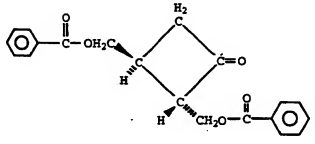
c) treating the cyclic orthoester product from step (b) with a Lewis acid catalyst to give the desired optically active cyclobutanone.

2. The process of Claim 1 wherein the osmium tetroxide in step (a) is employed in catalytic amounts by including 4-methylmorpholine, N-oxide as a cooxidant; the trimethyl or triethyl orthoester in step(b) is trimethyl orthoacetate;

the weak acid catalyst is step (b) is pyridium p-toluenesulfonate; and the Lewis acid catalyst in step (c) is boron trifluoride etherate, trimethylsilyl trifluoromethanesulfonate, boron trichloride, boron tribromide, diethylaluminum chloride, ethylaluminum dichloride, aluminum trichloride, titanium tetrachloride, tin tetrachloride, or tin trichloride.

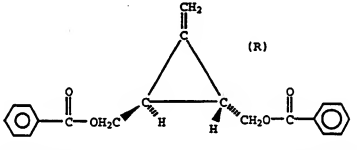
3. The process of Claim 1 or 2 wherein the Lewis acid catalyst in step (c) is boron trifluoride etherate.

4. A process for preparing the optically active cyclobutanone of the formula

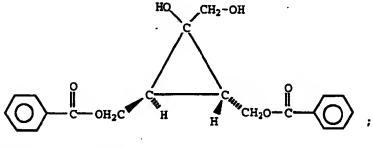


which comprises:

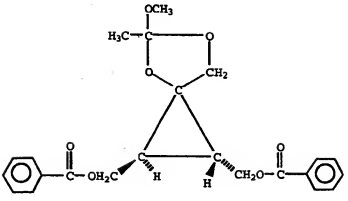
a) oxidizing the optically active 3-methylene compound of the formula



with an aqueous solution containing a catalytic amount of osmium tetroxide and 4-methylmorpholine N-oxide as cooxidant to give the optically active diol of the formula



b) converting the diol product from step (a) to the cyclic orthoester of the formula

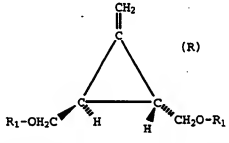


by treating the product from step (a) with trimethyl orthoacetate in the presence of pyridium p-toluenesulfonate; and

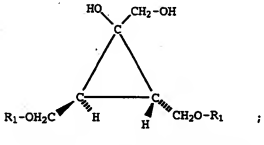
c) treating the cyclic orthoester product from step (b) with boron trifluoride etherate to give the desired optically active cyclobutanone.

5. A process for preparing the antiviral agent [1R-(1α,2β,3α)]-2-amino-9-[2,3-bis(hydroxymethyl)cyclobutyl]-1,9-dihydro-6H-purine-6-one which comprises:

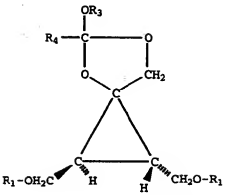
a) oxidizing the optically active 3-methylene compound of the formula



wherein R_1 is a hydroxy protecting group with osmium tetroxide to give the optically active diol of the formula



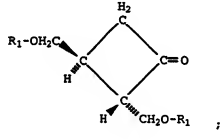
b) converting the diol product from step (a) to the cyclic orthoester of the formula



by treating the product from step (a) with a trimethyl or triethyl orthoester of the formula

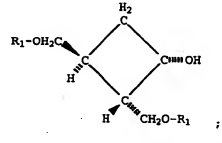
in the presence of a weak acid catalyst wherein R_5 is methyl or ethyl and R_4 is straight or branched chain alkyl or 1 to 6 carbons or phenyl;

c) treating the cyclic orthoester product from step (b) with a Lewis acid catalyst to give the optically active cyclobutanone of the formula



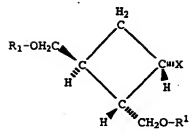
;

d) treating the optically active cyclobutanone product from step (c) with a reducing agent to give the optically active cyclobutanol of the formula



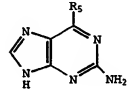
;

e) converting the optically active cyclobutanol product from step (d) to the optically active cyclobutane compound of the formula

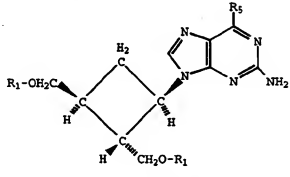


wherein X is a leaving group;

f) reacting the product from step (e) with the purine of the formula



to give the optically active compound of the formula

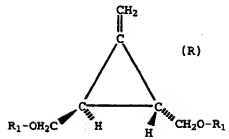


wherein R_5 is a group which can be converted into a 6-oxo substituent; and

g) treating the product step (f) to remove the R_1 hydroxy protecting groups and to convert the R_5 group to a 6-oxo.

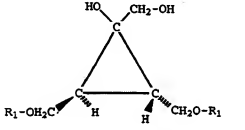
6. A process for preparing the antiviral agent [1R-(1α,2β,3α)]-2-amino-9-[2,3-bis(hydroxymethyl)cyclobutyl]-1,9-dihydro-6H-purin-6-one which comprises:

a) oxidizing the optically active 3-methylene compound of the formula



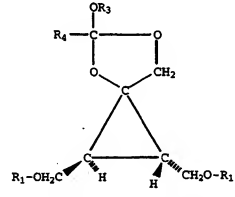
(R)

wherein R_1 is a hydroxy protecting group with osmium tetroxide to give the optically active diol of the formula



;

b) converting the diol product from step (a) to the cyclic orthoester of the formula

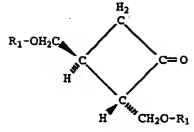


by treating the product from step (a) with a trimethyl or triethyl orthoester of the formula

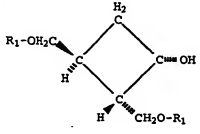
$$R_4\text{-}C\text{-}(O\text{-}R_5)3$$

in the presence of a weak acid catalyst wherein R_5 is methyl or ethyl and R_4 is straight or branched chain alkyl of 1 to 6 carbons or phenyl;

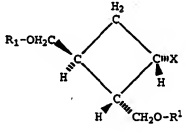
c) treating the cyclic orthoester product from step (b) with a Lewis acid catalyst to give the optically active cyclobutanone of the formula



d) treating the optically active cyclobutanone product from step (c) with a reducing agent to give the optically active cyclobutanol of the formula

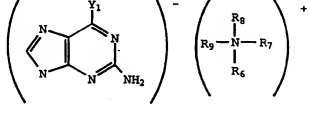


e) converting the optically active cyclobutanol product from step (d) to the optically active cyclobutane compound of the formula



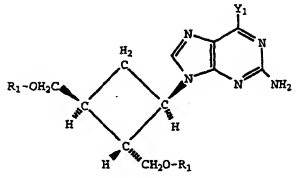
wherein X is a leaving group;

f) reacting the product from step (e) with the purine salt of the formula



wherein Y_1 is Iodo, bromo or chloro and R_6, R_7, R_8 and R_9 are independently selected from the group consisting of straight or branched chain alkyl of 1 to 10 carbons or substituted alkyl of 1 to 10 carbons wherein said

substituent is alkoxy of 1 to 6 carbons or aryl, to give the optically active compound of the formula

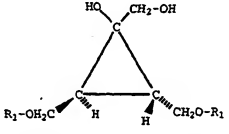


;

and

g) treating the product step (f) to remove the R_1 hydroxy protecting groups and to convert the Y_1 group to a 6-oxo.

7. A compound of the formula



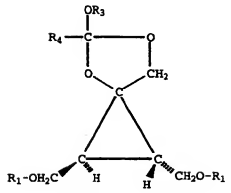
wherein R_1 is t-butyldimethylsilyl, t-butyldiphenylsilyl, (triphenylmethyl)dimethylsilyl, methyldiisopropylsilyl, triisopropylsilyl, benzyl, p-methoxybenzyl, triphenylmethiyl, 4-methoxy substituted triphenylmethyl, 4,4-dimethoxy substituted triphenylmethyl, or

;

and R_2 is straight or branched chain alkyl of 1 to 6 carbons or phenyl.

8. The compound of Claim 7, (1S-trans)-3-hydroxy-1,2,3-cyclopropanetrimethanol, α^1, α^2,-dibenzoate.

9. A compound of the formula



wherein R_1 is t-butyldimethylsilyl, t-butyldiphenylsilyl, (triphenylmethyl)dimethylsilyl, methyldiisopropylsilyl, triisopropylsilyl, benzyl, p-methoxybenzyl, triphenylmethyl, 4-methoxy substituted triphenylmethyl, 4,4-dimethoxy substituted triphenylmethyl, or

R_2 is straight or branched chain alkyl of 1 to 6 carbons or phenyl;
R_3 is methyl or ethyl; and
R_4 is straight or branched chain alkyl of 1 to 6 carbons or phenyl.

10. The compound of Claim 9, (1S,2S)-5-methoxy-5-methyl-4,6-dioxaspiro[2.4]heptane-1,2-dimethanol, dibenzoate.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 96 30 2173

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	EP-A-0 458 363 (E.R.SQUIBB & SONS,INC.) * page 51 - page 65; claims * ---	1-6	C07D473/00 C07C49/753 C07C49/517
A	EP-A-0 444 597 (NIPPON KAYAKU KABUSHIKI KAISHA) * page 3 * ---	1-6	C07C43/178 C07C43/23 C07C69/003 C07F7/18
A	EP-A-0 484 843 (E.R. SQUIBB & SONS,INC.) * page 13 - page 18; claims * ---	1-6	C07D317/72 A61K31/52
A	CHEMICAL ABSTRACTS, vol. 121, no. 13, 26 September 1994 Columbus, Ohio, US; abstract no. 157191c, page 980; column 1; XP002007760 * abstract * & JP-A-06 107 589 (NIPPON KAYAKU KK) ---	1	
A	CHEMICAL ABSTRACTS, vol. 119, no. 13, 27 September 1993 Columbus, Ohio, US; abstract no. 137552b, page 721; column r; XP002007761 * abstract * & JP-A-05 103 679 (NIPPON KAYAKU KK.) ---	1-6	TECHNICAL FIELDS SEARCHED (Int.Cl.6) C07D C07C C07F
A	EP-A-0 452 729 (ABBOTT LABORATORIES) * page 10 - page 15; claims * ---	1-6	
A	EP-A-0 335 355 (E.R. SQUIBB & SONS,INC.) * page 40 - page 48; claims * ---	1-6	
A	EP-A-0 322 854 (E.R. SQUIBB & SONS,INC.) * page 38 - page 46 * --- -/--	1-6	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	11 July 1996	Luyten, H

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CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

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European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 96 30 2173

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
D,A	EP-A-0 535 448 (E.R. SQUIBB & SONS,INC) * the whole document * & US-A-5 185 463 (E.R. SQUIBB & SONS,INC) ---	1-8	
D,A	EP-A-0 433 897 (E.R. SQUIBB & SONS,INC.) * page 11 - page 16; claims * & US-A-5 664 961 (E.R. SQUIBB & SONS,INC.) ---	1-6	
D,A	EP-A-0 572 209 (E.R. SQUIBB & SONS,INC,) * the whole document * ---	1-6	
D,A	EP-A-0 579 421 (E.R. SQUIBB & SONS,INC.) * page 20 - page 29; claims * -----	1-6	
			TECHNICAL FIELDS SEARCHED (Int.Cl.6)

The present search report has been drawn up for all claims

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D : document cited in the application
L : document cited for other reasons

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